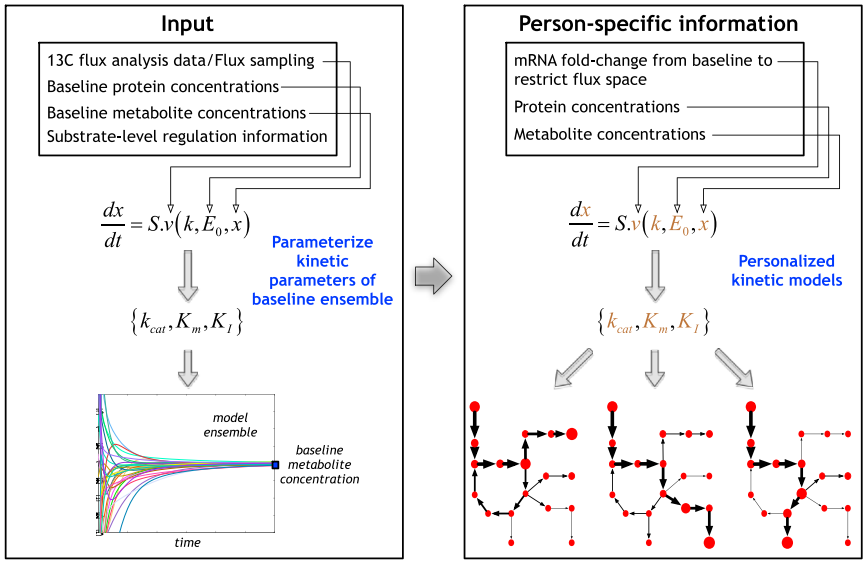

Figure 1. Construction of Individual-Specific Kinetic Models of Metabolism
Incorporation of multi-omics information in the dynamic concentration balances in the form of 13C metabolic flux data, baseline enzyme levels, metabolite concentrations as well as substrate level regulation could enable the parameterization (left) and personalization (right) of kinetic models of metabolism.

descriptions of metabolism, could provide the necessary tools in the future for parameterizing large-scale personalized kinetic models for monitoring individual health as well as suggesting pharmacological strategies compatible with the individual genotype. This will require careful parameterization of the kinetic models and confirmation of the proposed mechanisms of action.

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Global Edgetic Rewiring in Cancer Networks

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Two recent papers in *Cell* interpret lists of cancer genomic alterations in terms of how mutations rewire interactome networks.

The human genome project, conventional positional cloning efforts, and genome-wide association studies (GWAS), as well as exome sequencing and full genome sequencing of large numbers of tumors, have identified a nearly complete list of candidate human cancer genes. But how these genomic variants, sometimes referred to as the cancer "variome," lead to tumorigenesis remains obscure. To address this issue, work by Creixell et al. published in *Cell* describe new approaches for harnessing orthogonal data to functionally annotate a subset of the cancer variome (Creixell et al., 2015a; Creixell et al., 2015b). More importantly, these two papers put the cancer variome in the context of signaling networks to understand how individual cancer variations initiate network perturbations. These tools promise to advance our understanding of mechanisms of tumorigenesis, which in turn may provide leads for the development of novel effective therapeutic interventions.

Although lists of cancer mutations are critical to understand the genetic architecture of the cancer genome, it is increasingly appreciated that complex molecular networks and systems formed

by large numbers of interacting genes and gene products operate within and between human cells (Vidal et al., 2011). Systems and "interactome" networks are thought to exhibit emergent properties that cannot be understood by studying a single gene or gene product in isolation, and perturbations of such properties of complex cellular networks are likely to underlie most genotype-phenotype relationships, including those related to the pathogenesis of cancer. There is an urgent need for concepts, technologies, and a new generation of systematic datasets to functionalize and contextualize the cancer variome into predictive models of perturbed interactome networks.

Cancer research has made considerable progress in the last four decades with crucial conceptual shifts occurring along the way (Weinberg, 2014). The discovery of human oncogenes starting with *RAS* in the early 1980s followed a few years later by tumor suppressor genes such as *RB* firmly established cancer as a genetic disease. Another conceptual shift originated from the observation that the products of oncogenes and tumor suppressor genes interact both physically and functionally in the context of so-called cancer pathways. With the cancer variome in hand, it is now becoming possible to characterize all interaction perturbations in all cancer pathways in any cancer cell type and understand how interactome networks are globally rewired to lead to tumorigenesis.

Given the enormous complexity of such a task, it would make sense to start from a class of well-defined interactions such as those involving kinases and their substrates. A challenging goal would then be to annotate cancer alleles occurring in kinases and/or their substrates from the point-of-view of how such mutations affect kinase specificity, and this is exactly what the two papers by Creixell et al. have initiated.

In the first paper, a computational method referred to as "KINspect" is described to understand kinase-substrate interaction specificity at the level of individual protein residues. The authors noticed that when comparing the sequence similarity of whole kinase domains versus substrate motifs, no strong linear correlation could be found. They hypothesized that the lack of correlation might be due to the fact that not every residue in the kinase domain is responsible for substrate specificity. It turns out that the information is diluted when using whole domain sequences. To identify the critical positions within the domain, termed the determinants of specificity (DoS), the authors used a mask to weight each position to quantify the contribution of each residue to the substrate specificity, so that highly weighted positions could be regarded as determinants of specificity. To obtain the best mask with optimum predictive power of substrate specificity, a heuristic genetic algorithm was employed, which included a comparison to values determined experimentally by positional scanning peptide library (PSPL) screens. By using the specificity mask, the authors reported that the correlation could be enhanced by about 40%.

Notably, KINspect does not involve any artificial parameters, which allows the methodology to be potentially transferrable to other domains or other biological questions. Although no mechanism of how these positions determine kinase-substrate specificity was unveiled from this work, the pinpointed positions can serve as guideposts for follow-up studies, for example structure-based mechanistic studies or mutagenesis studies.

In the second paper, the authors integrated KINspect and other methods into a comprehensive platform referred to as ReKINect, by which a subset of the cancer variome can be annotated and categorized. These mutations are defined as network-attacking mutations or "NAMs" because they are thought to potentially perturb kinome signaling networks. Network-attacking mutations were separately classified into six basic categories, including genesis/extinction of phosphorylation sites, downstream/upstream network rewiring, and kinase activation/inactivation, using six different computational approaches combining different information sources. A number of interesting observations were derived from this analysis. For example, exome sequencing and proteomic data were combined to predict whether mutations can create or destroy phosphorylation sites. Determinants of specificity discovered by KINspect were used to identify kinase downstream rewiring mutations. Catalytically essential residues that mediate ATP binding, Mg^{2+} coordination, or phospho-transfer were used to predict kinase inactivation mutations. Although ReKINect was useful for analyzing a relatively small fraction of somatic cancer mutations, these two studies (Creixell et al., 2015a; Creixell et al., 2015b) undertook an integrative network approach that represents a huge leap forward toward the interpretation of heterogeneous cancer mutations.

This kind of multi-level integration and processing of network information will be crucial to interrogate how cancer variants affect interactome networks (Figure 1). Indeed, the functional consequences of most mutations remain unknown. What mutations are actually disease drivers? How do they increase the risk of disease? What underlies phenomena such as incomplete penetrance? These questions are still daunting challenges in cancer research. Answering them will require the development of both additional computational methods and novel high-throughput experimental strategies to functionalize and contextualize large numbers of putative cancer related mutations.

Such efforts have already been initiated in the context of addressing the extent to which human Mendelian disease mutations tend to lead to "node removal" or more subtle "edgetic perturbations" in the context of global interactome network models (in the lexicon of network biology, genes or gene products, and interactions between them are referred to as nodes and edges, respectively, and thus mutations that affect one or a few edges while leaving all others unperturbed have been named "edgetic alleles") (Zhong et al., 2009). A recent systematic characterization of thousands of Mendelian mutations has unraveled widespread specific macromolecular interaction perturbations, both at the level of binary protein-protein interactions and transcription factor binding interactions, across a large number of disease genes (Sahni et al., 2015). Although many Mendelian disease alleles can impact protein folding and/or stability, more than half appear edgetic in terms of biophysical interactions. This is in marked contrast to non-disease natural variants, which tend to retain most interactions mediated by the corresponding wild-type gene products (Sahni et al., 2015).

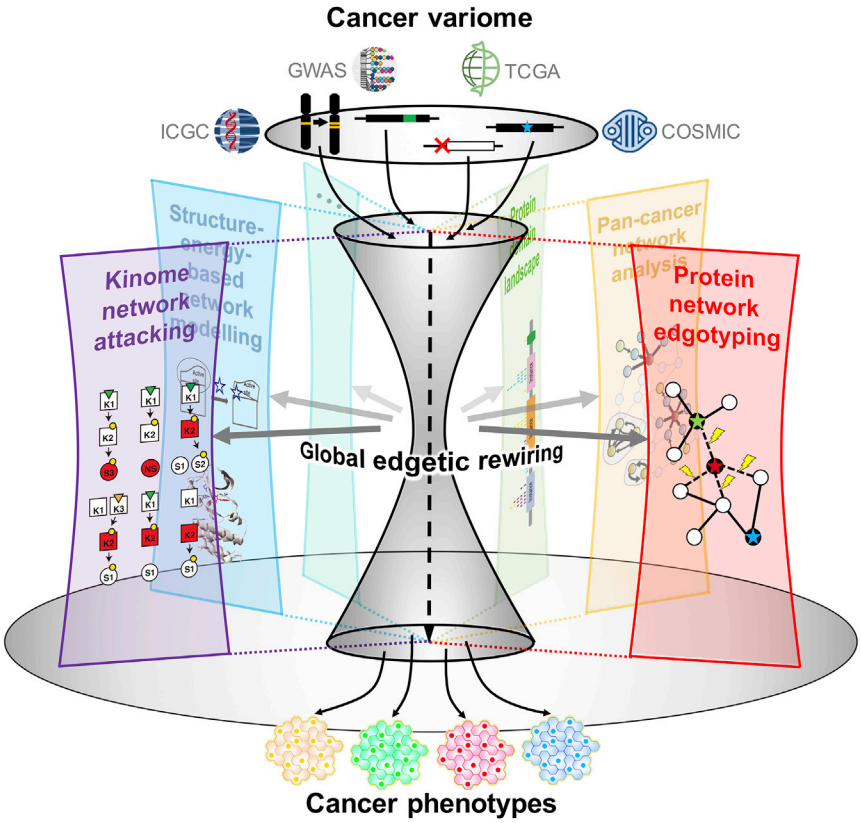

Figure 1. Edgetic Rewiring in Cancer Networks
One of the bottlenecks in cancer research is to understand how cancer variants result in tumorigenesis. One promising strategy to address this is to use global models of how edgetic mutations, which affect interactions between genes or gene products, rewire networks. Different colored boxes indicate distinct network-based profiles that are discussed in this Preview.

In addition to the kinase/substrate rewiring reported by Creixell et al., other approaches have been described to characterize the cancer variome from the point-of-view of global rewiring of cancer networks. For example, Wang et al. (2012) analyzed disease-related mutations in the context of a protein 3D structure network and found that in-frame disease mutations are significantly enriched on interaction interfaces and depleted outside domains. Kiel and Serrano (2014) took a step further to use structure-based energy calculations to estimate the effect of mutations on particular edges. Yang et al. (2015) and Miller et al. (2015) demonstrated how cancer mutations in distinct domains are likely to mediate different edgetic perturbations resulting in different tumor phenotypes and identified where the mutation hotspots reside in domains. Finally, Leiserson et al. (2015) developed a computational framework based on a directed heat diffusion model to identify subnetworks significantly mutated in cancer. Together, this body of work suggests that the bottleneck represented by the tens of thousands of uncharacterized cancer genomic alterations might be progressively cracked open by considering the variome in the context of network and systems models (Figure 1).

In this context, a "functional cancer variome project", utilizing a comprehensive collection of wild-type and mutant alleles, is urgently needed to empirically assess the effects of cancer mutations at an unprecedented scale on physical interactions, biochemical activities, and cellular assays. Examples would include but would not be limited to transcription factor binding, kinase and phosphatase assays, ubiquitination and de-ubiquitination assays, or acetyltransferase and deacetylase assays. Powerful computational prediction tools such as those described by Creixel et al. coupled with novel variome-wide experimental approaches will be necessary to determine which edges of interactome networks are perturbed in cancer and what the consequences of such perturbations might be in the context of global edgetic rewiring in cancer networks.

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